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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,064	01/29/2004	Tony Peled	24024-506	5661

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/767,064	PELED ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *201,209,212-214,238,239 and 244* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *201, 209, 212-214, 238-239 and 244* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment to the claims filed on October 30, 2007, has been received and entered. Claims 1-200, 202-208,210-211, 215-237, 240-243 have been canceled, while claim 201 has been amended. Applicants have also added claim 244 that is generally directed to elected invention

Claims 201, 209, 212-214, 238-239 and 244 are pending in the instant application.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/2007 has been entered.

Election/Restrictions

Applicants' election of claims 201, 209-215, 217-231, 235, 238 and 239 (Group I) in the reply filed on October 25 was acknowledged. Applicants have also elected culturing the cells in presence of one copper chelator (claims 201), neonatal umbilical cord cells (claim 209), FLT-3 ligand (claim 212) and granulocyte colony-stimulating factor (claim 214) as election of species for the elected invention. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Election was made without traverse in the reply filed on October 25, 2006.

Claims 201, 209, 212-214, 238-239 and 244 are under current examination.

Claim Objections

Claim 238 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. In the instant case, claim 238 limits the method of claims 201 to include hematopoietic mononuclear cells that are not enriched prior to culturing ex vivo cells, however, method of claim 201 recite the same limitation in the method steps including providing hematopoietic mononuclear cells that are not enriched prior to culturing. Thus, claim 238 fails to limit the subject matter of independent claim 201. Appropriate correction is required.

Claim Rejections- 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 201, 209, 212-214, 238-239 remain rejected under 35 U.S.C. 112, first paragraph, and newly added claim 244 is also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expanding an *ex vivo* population of CD34+ hematopoietic stem cell in culture, while at the same time inhibiting differentiation of the said cell ex vivo in culture medium; said method comprising:

(a) providing hematopoietic mononuclear cells that are not enriched prior to culturing , culturing said MNC *ex vivo* in culture under conditions allowing the proliferation and at the same time; said conditions for ex-vivo cell proliferation comprises providing either (i) early acting cytokines selected from the group consisting of stem cell factor, FLT3 ligand, interleukin-1, interleukin-2, interleukin-3, interleukin-6, interleukin-10, interleukin-12, tumor necrosis factor-a and thrombopoietin; and/or (ii) a late acting cytokines selected from the group consisting of granulocyte colony stimulating factor, granulocyte/macrophage colony stimulating factor, erythropoietin;and (b) culturing said MNC in presence of 5-10 μM copper chelator tetraethylenepentamineTEPA which reduces intracellular available copper concentration in said cells;

thereby expanding the population of said hematopoietic stem cell while inhibiting the differentiation of said HSC *ex vivo* in culture medium.

does not reasonably provide enablement for culturing mononuclear cells in presence comprising mixed population of cells under conditions comprising any copper chelator at any concentration, in an undefined medium as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants' arguments filed November 30, 2007 have been fully considered, but are not fully persuasive. Applicants argue that the state of the art with respect to the effect of copper chelators on the proliferation of hematopoietic stem cells is not unpredictable as argued by Examiner. Applicants assert that the skilled artisan would readily recognize that Percival does not provide any support to the Examiner's assertion that the use of various copper chelators in the claimed methods is unpredictable. Applicants assert that methods of culturing cells with copper chelators were well known in the art at the time of filing the instant

application, and an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance.

As an initial matter Applicants argument with respect to Percival et al that does not provide any support to the use of various copper chelators in the claimed methods is persuasive and therefore is withdrawn.

In response, it is noted that claims 201, 209-214, 238 and 239 embrace a method that uses culturing mononuclear cells in presence of at least one copper chelator. The specification has exemplified only culture medium supplement with chelator tetraethylpantamine (TEPA) in presence of right combination of cytokine result in effective expansion of HSC from the MNC. Peled et al (Exp Hematol. 2004; 32(6): 547-55) show that the only low-molecular-weight linear polyamine Cu chelator TEPA at a concentration that moderately reduced cell Cu content (by 20–30%) enabled extensive *ex vivo* expansion of $CD34^+$ cells in cultures supplemented with early-acting cytokines (see page 552). It is emphasized that specification acknowledges that while reducing the present invention to practice, it surprisingly and unexpectedly found that molecules such as copper chelator repress differentiation and stimulate and prolong proliferation of hematopoietic stem cells (see page 28, lines 26-30). The specification describes that copper chelate or chelators of the present invention is capable of forming an organometallic complex with a transition metal other than copper including zinc, cobalt, nickel, iron, palladium, platinum, rhodium and ruthenium (See page 54, para. 3 of the specification). In addition, specification also contemplated chelator is a polyamine chelating agent, such as, but not limited to ethylenediamine (page 66, lines 15-20). Thus, the breadth of copper chelator that reduces intracellular available copper concentration may be include EDTA, or citrate, that also chelate iron and cationic minerals necessary for cell proliferation. The specification does not teach how to extrapolate data obtained from $CD4^+$ cells ex-*vivo* assay studies using very specific transition metal chelator, TEPA to the development a method using any other

chelator for facilitating proliferation and inhibiting differentiation at the same time of hematopoietic stem or progenitor cells by culturing said cells in the medium with at least any copper chelator that reduces intracellular available copper concentration in said cell. As stated before post filing art of Peled (Experimental Hematology, 2004, Vol.32, pages 547-555) teaches that among various linear polyamine copper chelators only TEPA treatment has been currently shown to have an effects on ex-vivo expansion of CD34+ cells. The effects of others copper chelators are still under investigation (see entire document, page 552 in particular). In addition, prior to filing of instant application art generally recognized that polyaminic chelate could be toxic (Burgada et al., Eur.J Org. Chem, 2001, pages 349-352). The specification is additionally silent with respect to any teaching for culturing and expanding stem cells in the presence of any concentration of copper chelator or any combination of early and late acting cytokine that would facilitate expansion of CD34+ hematopoietic stem cell, while at the same time inhibiting differentiation of hematopoietic stem cell. Previously, Murray et al also emphasized the importance of the balance of cell cycling, division history, differentiation, and apoptosis of $CD34^+$ cells determines the net number of HSC produced in ex vivo cultures (see abstract). It is noted that single cytokines thrombopoietin (TPO), flt3 ligand (FL), and c-kit ligand (KL) each failed to increase the number of $CD34^+Thy\text{-}1^+$ cells, however, cultures including TPO, FL or TPO, KL gave the increase of $CD34^+Thy\text{-}1^+$ cell number. It is emphasized that considering the level of variation among the mobilized peripheral blood (MPB) samples, there was no significant difference among such cultures, which all resulted in maintenance or a small increase (1.2- to 1.5-fold) of $CD34^+Thy\text{-}1^+$ cell number. The cited art clearly indicate the importance of right balance to cytokine and nutrient combination and specific copper chelator concentration for optimal expansion of HSC as contemplated by the specification. This is further evidenced by Peters et al. (Br. J. Haematol, 119:792-802; 2002) who tested a large series of culture conditions, including those used

successfully with CB CD34+ cells, but only one of them sustained long-term, massive expansion of FL hematopoietic cells, reaching over $3xl0^7$-fold input cell number after · 150 days in culture. It is apparent that contrary to applicant's argument one of skilled in the art would have to make new discovery to determine right combination of early and late cytokine with appropriate concentration of copper chelator.

Thus, contrary to applicants' argument the issue is not whether methods of culturing cells with copper chelators were known at the time of filing of this application. Examiner would agree that method of expanding a population of cells including hematopoietic stem cells obtained from peripheral blood, bone marrow or neonatal umbilical cord blood (line 7, page 6), at the same time, for reducing a capacity of the cells in utilizing transition metal chelators such as copper chelator tetraethylenepentamine (TEPA; Figs. 1-5 and 20) (WO 99/40783 Peled et al. 8/19/1999) was known in prior art. As stated before, post filing art of Peled et al (Experimental Hematology, 2004, Vol.32, pages 547-555) discloses that among various linear polyamine copper chelators only TEPA treatment has been currently shown to have an effects on ex-vivo expansion of CD34+ cells. The effects of others copper chelators are still under investigation (see entire document, page 552 in particular). It is emphasized that neither specification nor prior art establishes any nexus between expansion of CD34+ cells in mixed population of cells (MNC) to presence of any copper chelator other then that exemplified in the instant application that reduces intracellular available copper to a level such that it facilitates expansion as well as inhibits differentiation at the same time of the CD34+ cells in a mixed population of cells. In the instant case, specification fails to show any representative number of structurally related compounds that in non toxic and could be used in the claimed method of ex vivo expanding a population of Cd34+ cells in a mixed population of cells, the artisan would not know the physical and chemical structure of a reasonable number of representative compounds falling

within the scope of the instant claims and consequently would not know how to make and use them particularly in view of toxicity associated with a number of polyaminic chelator (supra). It is emphasized that an experimentation to determine a copper chelator is not equivalent to a positive recitation of expansion of Cd34+ cells in a mixed population of cells.

The specific elements contemplated by the specification in the method of expansion of hematopoietic stem cells in presence of specific combination of cytokine and TEPA were not discovered by Applicant, rather they are derived from the prior art based on reports of their function in expansion of CD34+ cells . Absent of evidence to the contrary, it is not clear that other elements would be functional in the same manner as they have been demonstrated in the instant application. Thus, the art of record at the time of the invention does not provide enabling support for the claimed invention commensurate with full scope of the claims. It is noted that specific recitation of copper chelator that reduces copper concentration in the method of impendent claims would obviate the basis of rejection.

Withdrawn- Claim Rejections- 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 201, 209-214, 238 and 239 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 201, 209, 212-214, 238-239 and 244 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 201 recites the limitation "said hematopoietic stem cells" in the claim 201 (lines 10 and 11). However, method steps recite providing or culturing hematopoietic mononuclear cell and not hematopoietic stem cells. There is insufficient antecedent basis for this limitation in the claim. Claims 209, 212-214, 238-239 and 244 are also included in the rejection as they directly or indirectly depend on claim 201. Appropriate correction is required.

Claim 201 recites the term "and/or" in line 2. It is unclear what the metes and bounds of this term, as "and" could be interpreted to include only CD 133+ cells, or all of the cells, or, "or" would imply that the cell types are in the alternative. Appropriate correction is required. Claims 209, 212-214, 238-239 and 244 are also included in the rejection as they directly or indirectly depend on claim 201.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 201, 209, 212-214, 238-239 rejected under 35 U.S.C. 103(a) and newly added claim 244 is also rejected under 35 U.S.C. 103(a) as being unpatentable over Sandstrom et al (Blood. 1995; 86(3): 958-70, IDS) and Peled et al (WO99/40783, 8/19/1999, IDS) is withdrawn in view of applicants' argument as Sandstron do not teach a method that shows exapansion of CD34+cells. However, upon further consideration a new art rejection is presented below.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 201, 209, 212-214, 238-239 and 244 are rejected under 35 U.S.C. 103(a) and as being unpatentable over Fietz et al (Bone Marrow Transplant. 1999 Jun;23(11):1109-15) or Wang et al (Sheng Wu Gong Cheng Xue Bao. 2002 May;18(3):343-7)and Peled et al (WO99/40783, 8/19/1999, IDS).

Fietz et al teach a method to expand CD34+ hematopoietic by providing mononuclear cells that are not enriched prior to culturing the cells in presence of early and late acting cytokine to expand population of hematopoietic stem cells. It is noted that data shows overall increase in CD34+ cells is significant for the mononuclear cell fraction after one week of culture (see table 1). In addition, Fietz et al , specifically teach culturing the unseparated MNC fraction in culture medium containing SCF, IL-3, IL-6 , G-CSF , EPO and flt-3L (see page 1110, col. 1, para. 1) (limitation of claims 212-214). Wang et al teach a method wherein mononuclear cell (MNC) can be used to expand hematopoietic stem/progenitor cells by culturing cells in medium containing cytokine cocktails of SCF + IL-3 + IL-6 + FL + Tpo. Wang et al noted that the expansion of MNCs could be maintained up to 4 weeks which then declines after 4 weeks. Further the colony density and the proportion of CD34+ cells increased from day 0 to day 7 in the culture of MNC.

However, Fietz et al /Wang both differed from claimed invention by not expanding the culture of MNC or CD34+ cells in presence of a copper chelator.

Peled et al describe a method of expanding a population of cells including hematopoietic stem cells obtained from peripheral blood, bone marrow or neonatal umbilical cord blood (page 6, line 7,), at the same time, for reducing a capacity of the cells in utilizing transition metal chelators such as copper chelator

tetraethylenepentamine (TEPA; Figs. 1-5 and 20). It is noted that Peled et al also provided guidance that supplementing CD34+ cells with early acting cytokine and TEPA it is possible to maintain and expand long term culture by inhibiting/delaying the differentiation of CD34+ cells through chelation of transition metal (see page 27, see figure 19-21).

Accordingly, in view of the teachings of Fietz/Wang and Peled, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the method taught by Fietz/Wang by culturing MNC in presence of a copper chelator such as TEPA with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as Peled had already disclosed that CD34+ cell cultures with early-acting cytokines and TEPA, it is possible to maintain long term cultures (LTC) without the support of stroma (see example 2-3 and page 27). In addition, Fietz/Wang sought to examine the performance of MNC cultures supplemented with different combination of cytokines. Therefore, given that copper chelator such as TEPA was available for use to expand long term culture by inhibiting/delaying the differentiation of CD34+ cells through chelation of transition metal as per teaching of Peled, it would have been obvious for one of ordinary skill in the art to use copper chelator such as TEPA in the culture medium disclosed by Fietz/Wang with reasonable expectation of achieving predictable results of expanding CD34+ cell in culture of MNC.

One who would practiced the invention would have had reasonable expectation of success because Fietz/Wang had already described a method of *ex vivo* expansion of blood mononuclear cells (MNCs), in presence of early and late acting cytokine for one to four week, while Peled described use of copper chelator such as TEPA that could facilitate expansion of CD34+ cells beyond one week by inhibiting differentiation of CD34+ cells. Thus, it would have only required routine

experimentation to modify the method disclosed by Fietz/Wang to include TEPA in the culture medium as required by instant invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 201, 209, 212-214, 238-239 and 244 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 7,169,605. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 201, 209,

212-214, 238-239 and 244 of the instant application encompass a method of ex-vivo expanding stem and/or progenitor hematopoietic cells, while at the same time inhibiting differentiation of the stem/and or progenitor cells, comprising providing MNC and then culturing said cells in the presence of early and late acting cytokine and a copper chelator. Claims 1-11 of the '605 patent are directed to the same method steps, as that of the claims of the instant application. While the claims of the "605 patent do not specify culturing MNC cells that are not enriched, the specification of the '605 patent states: "main experimental strategies employed include incubation of mononuclear cells with or without selection of CD34+; with different cocktails of early and late growth factors; with or without serum" (col. 2, lines 17-22). Thus, it would be obvious for one of ordinary skill in the art to utilize the method claimed in the '605 patent to expand CD34+ cells to inhibit differentiation of CD34+ cells in mixed culture MNC. Thus, claims 1-11 of U.S. Patent No. 7,169,605and claims 201, 209, 212-214, 238-239 and 244 of the instant application are obvious variants of each other.

Claims 201, 209, 212-214, 238-239 and 244 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, and 8-17, 19-22, 131, 123-131 of copending U.S. Patent Application No.: 10,418,639. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 201, 209, 212-214, 238-239 and 244 of instant application encompass a method of ex-vivo expanding stem and/or progenitor hematopoietic cells, while at the same time inhibiting differentiation of the stem/and or progenitor cells, comprising providing MNC and then culturing said cells in the presence of early and late acting cytokine and a copper chelator. Claims 1-6, and 8-17, 19-22, 131, 123-131 of the application no 10,418,639 are directed to the same method steps, as that of the claims of the

instant application. While the claims of the '639 application do not specify culturing MNC cells that are not unselected, the specification of the '639 application states: "the results illustrates the effect of TEPA chelator on the expansion of CD34+ cells in a culture of mixed hematopoietic cells" (see Fig 16-18). Thus, it would be obvious for one of ordinary skill in the art to utilize the method claimed in the '639 application also embraces to expand CD34+ cells to inhibit differentiation of CD34+ cells from a mixed culture of MNC. Thus, claims 1-6, and 8-17, 19-22, 131, 123-131 of the application no 10,418,639 and claims 201, 209, 212-214, 238-239 and 244 of the instant application are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 201, 209, 212-214, 238-239 and 244 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2-11, and 23 of copending U.S. patent Application No.: 10/564777 . Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 2-11, and 23 of the '777. Application are directed to a method of expanding an *ex-vivo* population of hematopoietic stem cells, while at the same time, substantially inhibiting differentiation of the hematopoietic stem cells ex-vivo, the method comprising hematopoietic mononuclear cells that are not enriched prior to culturing; culturing said mononuclear cells ex-vivo under conditions allowing for cell proliferation, said conditions comprising providing nutrients and at least an early acting cytokine or cytokines and, at the same time, culturing said mononuclear cells in the presence of at least one copper chelator capable of reducing intracellular available copper concentration in said cell or chelate; and wherein the cells are proliferated in the presence of FLT3 ligand. It is noted that "777 incorporates by references a prior application teaching the promotion of long term ex vivo stem cell proliferation,

while inhibiting differentiation, using TEPA-Cu chelates as well as the chelator TEPA using as a starting population an un-selected peripheral mononuclear fraction. The results described there-in clearly show that stem and progenitor hematopoietic cells may be substantially expanded ex vivo, continuously over at least 12 weeks period, in a culture of mixed (mononuclear fraction) blood cells, with no prior purification of CD34+ cells.

Therefore, to practice the instant invention, it would have been obvious to utilize the method claimed in the '777 application. Thus, claims1, 2-11, and 23 of U.S. Patent Application No.: 10/564777 and claims 201, 209, and 212, 213 and 238 1, 2-11 and 23 of the instant application are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh, Ph.D.
AU 1632

/Thaian N. Ton/
Primary Examiner
Art Unit 1632